Fine-Needle Aspiration Cytology of Noninvasive Follicular Variant of Papillary Thyroid Carcinoma is Cytomorphologically Distinct from the Invasive Counterpart

Running Title: FNA Cytology of NIFTP

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Abstract

Objective:

To review a series of noninvasive encapsulated follicular variant of papillary thyroid carcinomas (FVPTC) in an attempt to further define the role of cytopathology in the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and invasive FVPTC.

Methods:

Surgical pathology cases diagnosed as FVPTC with correlating thyroid fine needle aspiration (FNA) were identified and divided into two FVPTC groups: noninvasive and invasive. Cytologic diagnoses were compared between them.

Results:

We identified 23 cases that met the criteria for noninvasive FVPTC, and 27 cases that were typical infiltrative FVPTC (16) or encapsulated FVPTC with either capsular and/or lymphovascular invasion (11). Of the noninvasive FVPTC cases, there were 4 benign, 14 follicular lesions of undetermined significance (FLUS), 4 follicular neoplasms (FN), 1 suspicious (S), and no papillary thyroid carcinomas (PTC). In the invasive FVPTC group, there was no benign, 4 FLUS, 3 FN, 12 suspicious, and 8 PTC cases.

Conclusions:

There is a distinction on the cytologic diagnosis between noninvasive and invasive FVPTC. The invasive subtype was diagnosed by FNA as suspicious for PTC or PTC in nearly 75% of cases while only 1 case (4%) for the noninvasive subtype was diagnosed as suspicious for PTC ($p<0.05$).

Introduction

Ultrasound-guided fine-needle aspiration biopsy (FNAB) is the recommended modality for the evaluation of suspicious thyroid nodules. Since the introduction of FNAB, the incidence of thyroid carcinoma has nearly tripled.(1) At the same time, however, disease mortality has remained constant.(1) This paradox is attributed to the fact that we are diagnosing many more nonfatal cases, of which most are minimally invasive and minimally malignant tumors.(2) The noninvasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC) falls into this category and numerous studies have demonstrated that this variant is unique in both its clinical behavior as well as its molecular profile.(3-5) It is now well documented that invasion correlates with clinical outcome in encapsulated tumors and the noninvasive FVPTCs can be managed clinically as follicular adenomas.(6, 7) Therefore, the Endocrine Pathology Society Working group on encapsulated FVPTC has proposed that these lesions be re-categorized as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is nearly widely used when reporting thyroid cytopathology and each category has a known implied risk of malignancy and recommended clinical management.(8) As expected, reclassifying noninvasive FVPTC as NIFTP will have an impact on the rate of malignancy for each of TBSRTC categories. Faquin et al recently published data showing that this reclassification would have the most impact on the 3 indeterminate categories of TBSRTC: the atypia of undermined significance/follicular lesion of undetermined significance (AUS/FLUS) category would have a decrease risk of malignancy of 5.2% to 13.6%, the follicular neoplasm (FN) category would have a decrease risk of malignancy

of 9.9% to 15.1%, and the suspicious (S) category would have a decrease risk of malignancy of 17.6% to 23.4%.(9) This data reiterates the findings of a previous study by Strickland et al which concluded that if the terminology were changed, the rates of malignancy for FNA diagnostic categories would be decreased.(10)

This re-classification will theoretically help reduce the pressure felt by clinicians to treat "borderline" cancers and cytopathologists alike could practice with "reduced concern for minimal cytologic findings that lead to the overuse of the AUS/FLUS category."(11) As such, we have reviewed a series of FVPTCs in an attempt to further define the role of cytopathology in the diagnosis of NIFTP and invasive FVPTC.

Materials and Methods

This study was approved by the Indiana University Institutional Review Board. A computerized search of our pathology laboratory information system was performed to identify all surgical pathology diagnosed as FVPTC with correlating thyroid FNAB at our institution for the 5-year period from 2010 through 2014. FNAB cases were categorized using TBSRTC.

Patient data were collected and included the age and sex, the size and location of the sampled nodule, and the surgical follow-up. Only cases where the resected nodule correlated with the nodule sampled by FNAB were included in our study.

The cytologic and surgical pathology reports as well as pertinent clinical history and radiographic results were reviewed. The air-dried (modified Wright-Giemsa stained) and ethanol fixed (Papanicolaou-stained) direct smears from the thyroid aspirates and the histologic

slides of the corresponding surgical resections were reexamined independently by both authors. The authors were blinded to the surgical pathology diagnoses at the time of the review. Both authors then sat at a double microscope to resolve any discrepancy. Based on the histology from the surgical resection specimens, cases were divided into two groups: cases that meet the criteria for NIFTP (noninvasive FVPTC) and invasive FVPTC. The noninvasive group was defined by tumors with papillary thyroid carcinoma-like nuclear aberrations (as opposed to follicular adenomas which lack this nuclear atypia) with a well-defined growth pattern with a total or partial fibrous capsule and were negative for capsular and/or lymphovascular invasion or extrathyroidal extension. Invasive FVPTC cases included an infiltrative type of FVPTC (unencapsulated tumors with infiltrative features and conventional papillary nuclear features) and an encapsulated FVPTC with capsular and/or lymphovascular invasion. Cytologic diagnoses were compared between the two groups. Statistical analysis using the chi-square test was performed through a web calculator (http://www.socscistatistics.com/tests/chisquare/Default.aspx). Statistical significance is set at 5% ($P<0.05$).

Results

A total of 287 surgical pathology cases were identified, of which 50 had correlating FNA samples. All FNAB cases were adequate for evaluation. Of the 50 cases, 23 cases met the criteria for noninvasive FVPTC, 16 cases were typical infiltrative FVPTC and the remaining 11 cases were encapsulated FVPTC with either capsular and/or lymphovascular invasion. Only two of 16 cases of infiltrative FVPTC showed coexisting angiovascular invasion.

In the noninvasive FVPTC group, ages ranged from 30-81 and the male to female ratio was 3:20. Tumor sized ranged from 0.4-5.1 cm with a median size of 1 cm and an average size of 1.3 cm (n=27). In the invasive FVPTC group, ages ranged from 25-69 and the male to female ration was 6:21. Tumor sized ranged from 0.3-7.2 cm with a median size of 1.6 cm and an average size of 2 cm (n=23). Of the noninvasive FVPTC cases, 4 (17%) were diagnosed as benign (B), 14 (61%) were diagnosed as follicular lesion of undetermined significance (FLUS), 4 (17%) were diagnosed as follicular neoplasm (FN), 1 (4%) were diagnosed as suspicious (S), and none were diagnosed as papillary thyroid carcinoma (PTC). In the invasive FVPTC group, none was diagnosed as B, 4 (15%) cases were diagnosed as FLUS, 3 (11%) cases were diagnosed as FN, 12 (44%) cases were diagnosed as suspicious, and 8 (30%) cases were diagnosed as PTC (Table 1). The invasive subtype was diagnosed by FNAB as suspicious for PTC or PTC in nearly 75% of cases while only 1 case (4%) for the noninvasive subtype was diagnosed as suspicious for PTC ($p<0.05$). 61% of cases diagnosed as FLUS turned out to be noninvasive while only 15% were invasive ($p<0.05$).

Discussion

FVPTC represents a large portion of PTC cases and appears to be increasing in incidence. (9, 12-14) Noninvasive FVPTC comprises a significant portion of the FVPTC diagnoses.(9, 13, 14) The importance of recognizing the distinction between the invasive and noninvasive counterpart has become clearer over the past decade since we now know that the noninvasive FVPTC behaves in a distinctly indolent manner and can be treated as a follicular adenoma.(6, 7) While

the distinction between these two counterparts is easily recognized on the histologic level, the differences between the two on the cytologic level is often undervalued.

At our institution, noninvasive FVPTC was most often categorized as FLUS by FNAB, representing 61% of the cases. The second most common FNAB diagnosis was benign (17%). In contrast, invasive FVPTC was diagnosed as suspicious for PTC in 44% of cases and as outright PTC in 30% of cases. Moreover, none of the cases of noninvasive FVPTC were diagnosed as PTC and none of the cases of invasive FVPTC were diagnosed as benign.

Our data suggest that there is a cytomorphologic distinction between noninvasive FVPTC and invasive FVPTC. The invasive subtype, encompassed both infiltrative and encapsulated FVPTC with either capsular or angiovascular invasion, was diagnosed by FNAB as suspicious for PTC or PTC in nearly 75% of cases while only 1 case (4%) for the noninvasive subtype was diagnosed as suspicious for PTC. It is our impression that the invasive variant showed more obvious diagnostic nuclear aberrations (Figure 1). The invasive variant also tends to have higher cellularity of atypical cells with easily identifiable nuclear irregularity, grooves, and pseudoinclusions, leads to a more definite cytologic diagnosis (suspicious for PTC or PTC). Cases of noninvasive FVPTC displayed only subtle nuclear changes and were overall less cellular. A more thorough, high-power examination was required to spot the nuclear aberrations. The nuclear aberrations often included subtle nuclear grooves or minor nuclear enlargement. Nuclear pseudoinclusions were not easily identified. The nuclei of non-invasive variant tend to be more rounded and less irregular than the invasive type (Figure 2). It is our impression that while individual cytologic features cannot be used as a predictor of invasion, the overall

cellularity and ease of identifying the atypia in the individual cases (leading to diagnoses of FLUS versus suspicious) is important. Cases diagnosed as FLUS were much more likely to fall into the noninvasive camp, 61% versus 15% of the invasive variant. The proportion of cases diagnosed as FN was similar in both groups (3 cases for invasive vs. 4 cases form non-invasive type).

Overall we note a clear difference in FNA diagnoses between noninvasive FVPTC and invasive FVPTC. We found that the median size of those lesions that turn out to be noninvasive is 1 cm compared to 1.6 cm in those that fell into the invasive camp. This size difference could account for higher cellularity due to more accurate sampling in the larger lesions and allowing for a more definitive diagnosis.

Additionally, at our institution, we use fairly strict criteria for a suspicious diagnosis. Our risk of malignancy for suspicious is 93% (5-year review of 2531 cases, unpublished data, including papillary microcarcinoma) and will be 90% if excluding NIFTP. Cases that reveal only focal or less convincing cytologic features of papillary carcinoma are classified as FLUS or FLUS cannot exclude papillary carcinoma (risk of malignancy is 36% for FLUS including papillary microcarcinoma and 27% if excluding NIFTP). This could account for the discrepancy we saw in our data compared to other published data.

Our data shows that at our institution FNA is clearly an effective method to identify invasive FVPTC. An FNA diagnosis of suspicious for PTC or PTC has a high likelihood of being an invasive

FVPTC. An FNA diagnosis of FLUS is encountered much more often in noninvasive FVPTC and, thus, a more conservative clinical management approach should be favored. Ancillary molecular testing for BRAF and RAS might be warranted in this setting.

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Figure legends

Figure 1. FNA cytology of invasive FVPTC demonstrating characteristic cytologic feature of papillary carcinoma. (**A**) Tumor cells show oval nuclei with nuclear enlargement, overlapping, irregular nuclear membrane, intranuclear pseudoinclusion (Papanicolaou staining, x400), (**B**) frequent nuclear grooves (Papanicolaou staining, x400), and (**C**) dense colloid in the background (Diff-Quik staining, x400).

Figure 2. FNA cytology of noninvasive FVPTC. (**A**) Nuclei are mildly enlarged, with less membranous irregularity and nuclear overlapping (Diff-Quik staining x400). (**B**) Nuclear grooves are not as frequent (Papanicolaou staining, x 400).